

Status of Airway Reactivity among Small Airway Diseases with Regular Users Substance Abuse of Inhaling Opium; Preliminary Results of a Survey of Indirect Provocation Test

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A B S T R A C T

Background: Opium is an oldest recreational abuse substance with dependency. Small airway diseases (SAD) were established within opium user's population. Bronchial hyper-responsiveness (BHR) reflects airway reactivity and inflammation. Opium can induce airway inflammation and following airway reactivity. The objective of the study assessed status of BHR among SAD with regular inhaled opium users. It performed with hypertonic normal saline provocation challenge test.

Methods: Target population enrolled among SAD with inhaled regular opium users. In the next step, standard hypertonic normal saline provocation test carried out on the sample study.

Results: A total of 46 subjects followed the study. The mean age $\pm$ SD was 50.1 $\pm$ 1.2 years, with median 48 years. 91% of those were male. A positive result of BHR was distributed more frequently in the chronic obstructive pulmonary disease (COPD) with the asthma phenotype. In addition, it was more market in the youngest and advanced age classes equally.

Conclusion: hypertonic normal saline provocation test result was quite noticeable between regular inhaled opium users. BHR was detected more frequently in COPD with asthma phenotype, COPD, chronic bronchitis, and bronchial asthma disease, respectively. The outcome indirectly revealed that there was a relation between airway inflammation and opium inhalation in population. It may be reflected an added effect on the predisposing risk factors of induced airway inflammation and hyper-reactivity of airway in target populations.

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► *Implication for health policy/practice/research/medical education:* Airway Reactivity among Small Airway Diseases with Regular Users Substance Abuse of Inhaling Opium

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1. Introduction:

Opium is one of the member substance abuse families. It is a substance extracted from Poppy. Using history of it comes back to the antiquity. Opium was applied in traditional medicine and in Iran named as Afion or Taryak (1). Substances have been used as recreational propose in the world. Harmful uses of any substances wiche are not approved by medical references, defined as substance abuse (2).

Opium is practiced habitually for pain relief and before sexual contact in middle-aged people. Prevalence of opium users was 18% in Iranian adults (3). It consumes as inhalation or comestible. Small airway diseases were reported among opium user population. The first published of association between opium and chronic obstructive pulmonary disease (COPD) reported from Tehran in 1976 (4). Opium smokers can be clinically demonstrated the lung diseases with an obstructive pattern (5). The effect of opium on respiratory system has not been evaluated clearly. It can induce chronic bronchitis, emphysema, bronchiolitis and COPD (4, 5). Evidences indicated that the opium inhalation can be enumerated as a risk factor in COPD epidemiology (5).

There is overlapped between asthma and COPD (5) both can be presented with fixed airway obstruction (6). However, asthma encountered as a risk factor for development of COPD (5, 7). Bronchial hyper-responsiveness (BHR) is a hallmark

of asthma and it can be detected in 54% of the COPD patients (8). Opium has adverse effects on the asthma and COPD. It raised mortality rate in airway obstructive diseases (9).

The aim of this study was assessed status of BHR among SAD with regular inhaled opium users.

2. Materials and Methods:

This study was cross-sectional, descriptive. It conducted in the Shahid Beheshti University of Medical Sciences (SBUMS), Loghman Hakim general teaching hospital, in 2013, Tehran, Iran.

Sample population enrolled among substance abuse opium with inhalation method.

SAD subsets, COPD, bronchitis and asthma definition applied on the focus population. In the next step, SAD diagnosed based on the global initiative for obstructive lung disease (GOLD) criteria (11) and American Thoracic Society (ATS) (12) asthma guideline. Indirect Provocation challenged test (IPCT) performed after establishment of SAD subsets.

Definition of COPD is consists of symptoms such as cough, sputum and dyspnea, airway obstruction pattern and irreversible airflow limitation. The standard criteria for spirometric pattern is include $FEV_1/FVC < 0.70$. Irreversibility of airway assessed based on the response of airway to the bronchodilatory effect of salbutamol (β_2 -agonist). It defined as the response rate, $FEV_1 < 12\%$ or less than 200cc.

Bronchial asthma disease is defined as tracheobronchial airway tracts inflammation. It characterized with bronchial hyper reactivity, reversibility airway obstruction and induced with multifactor's stimulants. Asthma

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diagnosed based on the obstructive spirometry pattern and complete reversibility of airway tracts $FEV_1 > 12\%$.

Bronchitis is an inflammatory respiratory tracts disease. It is detected in the clinical features. Productive cough presented in the three months in two consecutive years. Provocation challenged test (PCT) is a standard test for diagnosis of airway reactivity and gold standard test in diagnosis of asthma. It performed with direct (Methacholine) and indirect (Hypertonic saline) methods. The former test was associated with raised risk of complications in our subjects.

Hypertonic saline PCT (HPCT 4.5%) was delivered to patients with an ultrasonic nebulizer in the progressively increased interval period (0.5, 1, 2, 4 and 8 minutes). Accepted test result defined with a 20% decreased FEV_1 respect to basic value (13).

Tobacco smoking was accompanied with opium inhalation. All the subjects were smoker. Regular opium user defined at least three times a week. Opium inhalation method was prominent route of using opium 95%. They were also consumed other product of opium such as sokhteh. The recent is remained after opium smoked and used orally.

Patients should be stop medications that decrease bronchial response before the HPCT in defined time protocol (short medium and long acting bronchodilators, oral bronchodilators, cetirizine, hydroxyzine, leukotriene modifiers, cromolyn and food (Tea, Coffee, Chocolate).

Include criteria was consisted of sex (just males), regular opium inhaled (3-5 times /week), opium user duration over five years and SAD subsets.

Exclude criteria was consisted of low $FEV_1 < 1.5$ L or $< 60\%$., predicted value in the adults, serious airway obstruction $FEV_1 < 50\%$ or 1 L, exacerbation state of COPD, cardiovascular problems (13), heart attack or stroke < 3 months, known aortic aneurism, uncontrolled

hypertension, severe hypertension 200/100 mmHg.

SPSS 19 program was used for analyzed data. Frequency was presented with percent. Normality test of Kolmogorov-Smirnov and Shapiro-Wilk were $P < 0.05$. Compare of means were carried out with nonparametric tests such as; crosstabs and chi-square. Association was performed with chi square test; phi and Cramer's v and fisher's exact test. Significant value was $P < 0.05$ in through the study (two tailed).

3. Results:

A total of 46 subjects followed entrance criteria. The mean age $\pm$ SD was 50.1 ± 1.2 years. The ranged of them were 31-69, Median 48, and Mode 48 years. Sex's frequency was males 91% and females 9%. Figure 1 shows distribution of age classes' frequency.

HPCT was the positive outcome in 91% of the samples study. It was marked in male. However, it was more frequently distributed within advanced age class and first young class. Figure 2 displays the frequency distribution of IPT resulting respect to age classes. Fisher's exact test was performed between sex and HPCT results. It was significant ($P < 0.001$). In addition, there were suggestive differences between sex and HPCT results in Phi and Cramer's v tests ($P < 0.001$).

Subsets of SAD were COPD with asthma phenotype 48%, COPD 28%, Bronchitis 20% and Asthma 4%, respectively. Figure 3 presents the frequency of HPCT outcome within SAD subtypes. HPCT was noticeable in the COPD with the asthma phenotype. Spearman's rho was detected markedly correlation between SAD subtypes with HPCT ($r = 0.4$, $P < 0.02$). There were relevant differences between SAD subtypes with HPCT ($\chi^2 < 0.03$).

4. Discussion:

Opium has a footprint on the Sumerian clay tablet (2500 BC) (14). Frequency of using opioids has the third position in the world (15). Opiates are one of the popular substance abuse. It is estimated that over 12-21 million people are user in the world (14). Southwest Asia has a high rate of consumption (16). Iran has a prevalent rate of dependency opiate drugs up to one

million (14). Opium inhaled over 95% by Iranian people (17).

Our outcome of the study indicated that there was relation between BHR and regular opium inhaler cases. COPD and related disease as COPD with asthma phenotype and bronchitis were the more frequency of the focus population. The result may be followed with suggested evidence.

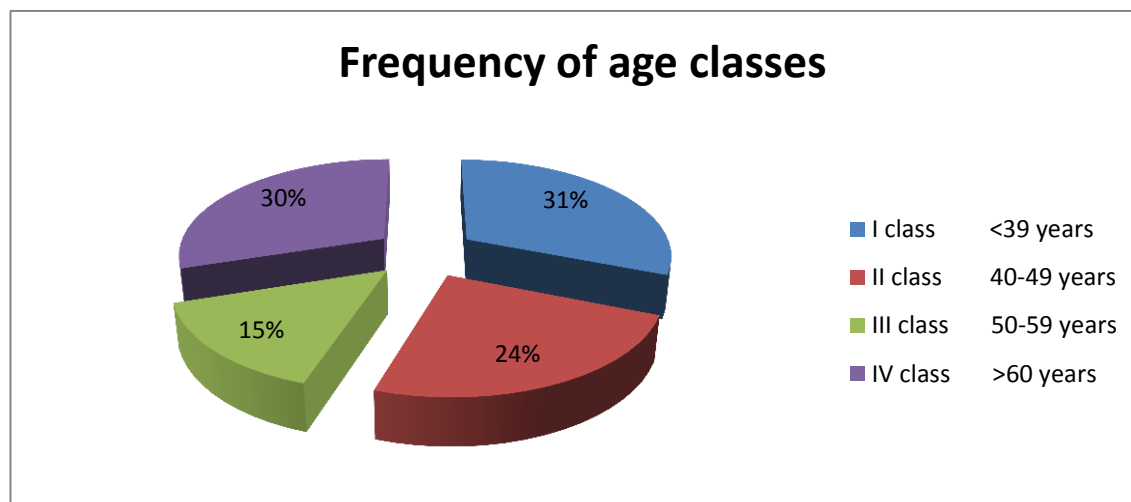


Fig. 1. It shows distribution of age classes' frequency.

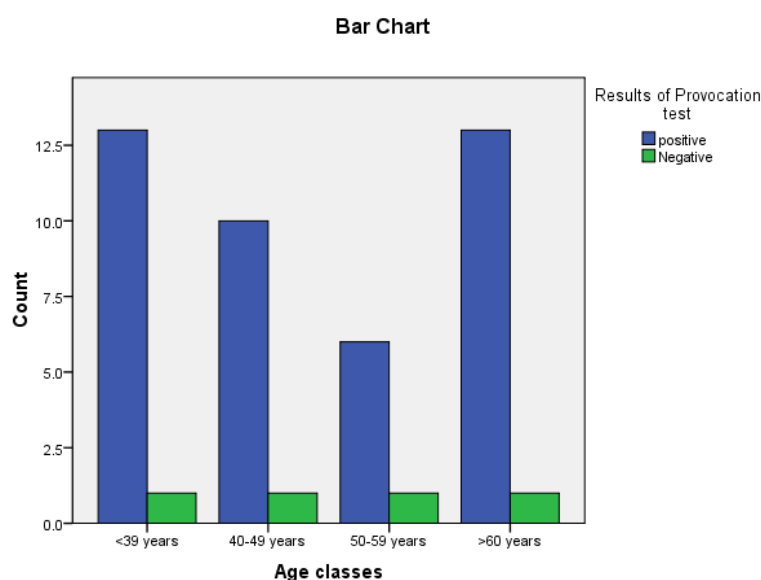


Fig. 2. It displays the frequency distribution of hypertonic normal saline provocation challenge test resulting respect to age classes.

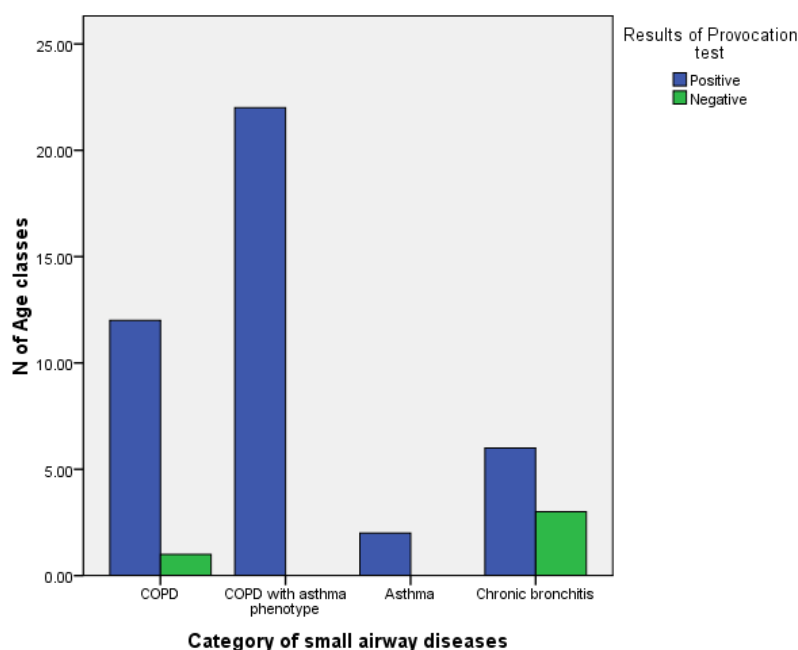


Fig. 3. It presents frequency of hypertonic normal saline provocation challenge test outcome within small airway disease subtypes.

BHR is an excessive response of narrowing of airway to the provoking stimulus that detected with bronchial provocative challenged test (PCT). It was performed direct and indirect, according to the broncho constriction mechanism. Direct PCT was performed with Methacholine. It causes contract with smooth muscles of respiratory tracts directly through stimulation of muscarinic M3 receptors. The response of the MPT is occurring as fixed and variable patterns. Fixed response reflected persistent structural and functional airway changes that may be associated with inflammation (18, 19). Conversely, variable pattern is rapid, increased rate of BHR reaction and related to the inflammation.

Indirect PCT was carried with osmotic agents (hypertonic saline). It acts on the specific receptors of adenosine monophosphate on the mast cells. A2b receptor is stimulated and released mediators such as histamine, leukotrienes and prostaglandins with cross linking IgE antibodies, and that leads to contraction smooth muscles (20). Hypertonic saline

PCT reflects inflammation and mast cells in the airways. Magnitude of the response to indirect PCT was related to the greater numbers of the mast cells in the airway epithelial (21). However, opium alkaloid is a histamine liberator (22).

BHR is the hallmark of asthma disease. In addition, it detected in the healthy subjects (23), COPD (21) and other non-pulmonary diseases (24). BHR is linked to the airway inflammation with either neutrophilic or eosinophilic originated inflammations. It increased mortality risk in adults (25). However, COPD subjects are at great risk of mortality based on the age-related of disease, degree airflow obstruction and intensity of bronchial hyper reactivity (26).

Prevalence of BHR in COPD patients reported 63% in male and 87% in female(27). Smoking habit is the main risk factor in development of COPD. Exposure against smoke has associated with development and increased of BHR (28). Its severity was dosed –depended and time –related (29).

COPD is one of the subset of SAD and usually developed among opium user population. In recent decade, there were overlapped conditions between COPD and asthma; as presented of BHR and rate of reversibility airways. It defined as overlap phenotypes; COPD with asthma-like phenotype (30). Regular opium smoking can affect on the immune function. It induced responses of pro-inflammatory mediating cytokines in serum (31). However oxidative stress mechanism was mild to moderately active in association with inflammation between opium smoker subjects (32). It is known mechanism in the development of COPD. Effect of opium on the airway system was not evaluated clearly. Current evidence is probably the similar founded mechanisms in the induction of airway inflammation (33).

Recent report indicated that cytokine secretion of lymphocytes in opium addictions were lower than a control grouped. The results may be explained the increased frequent microbial infection in the target population (34). Cigarette smoke has a depressed effect on the protective function of airway's mechanism (35). It may be seen in the using of opium as smoking manner. Susceptibility to microbial infection in the lung (microbiome) increased chronic inflammation and has even seen in the COPD patient in the stable condition (36). The mentioned concepts may be an influence in the development or induced airway BHR.

In conclusion; hypertonic normal saline provocation test result was quite noticeable between regular inhaled opium users. BHR was detected more frequently in COPD with asthma phenotype, COPD, chronic bronchitis and bronchial asthma disease, respectively. The outcome indirectly reflected relevant of airway inflammation within opium inhalation population. It may be reflected an added effect on the predisposing risk factors of induced airway inflammation and hyperreactivity of airway between target populations.

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